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## **CRIM-negative infantile Pompe disease: 42-month treatment outcome**

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# CRIM-negative infantile Pompe disease: 42-month treatment outcome

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**Abstract** Pompe disease is a rare lysosomal glycogen storage disorder characterized by deficiency of acid  $\alpha$ -glucosidase enzyme (GAA) and caused by mutations in the *GAA* gene. Infantile-type Pompe disease is a multi-organ disorder presenting with cardiomyopathy, hypotonia, and muscular weakness, which is usually fatal. Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) has recently been shown to be effective and subsequently yielded promising results in cross-reactive immunologic material (CRIM)-positive patients. CRIM-negative patients showed a limited response to ERT and died or were ventilator dependant. Over a period of 44 months, we monitored cognitive and motor development, behavior, auditory function, and brain

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elucidated; however, this is the first report presenting a ventilator-free survival of a CRIM-negative patient beyond the age of 36 months. The central nervous system (CNS) findings are hypothesized to be part of a yet not fully described CNS phenotype in treated patients with longer survival.

### Abbreviations

ERT enzyme replacement therapy  
MRI magnetic resonance imaging  
CNS central nervous system  
GAA acid  $\alpha$ -glucosidase

### Introduction

Pompe disease (glycogen storage disease type II, MIM #232300) is a rare, progressive, metabolic neuromuscular disorder resulting from lysosomal acid  $\alpha$ -glucosidase (GAA) deficiency (Hirschhorn and Reuser 2001) inherited as an autosomal recessive disease. The phenotype of Pompe disease is heterogeneous and primarily characterized by accumulation of glycogen in skeletal and cardiac muscle associated with progressive skeletal muscle weakness in all variants of the disease and by rapidly progressive hypertrophic cardiomyopathy and early death at about the age of 1 year in patients with the severe infantile variant (Hirschhorn and Reuser 2001; Kishnani and Howell 2004; Kishnani et al. 2006a). Glycogen accumulation, however, has also been well documented in central (CNS) and peripheral (PNS) nervous systems (Gambetti et al. 1971; Mancall et al. 1965; Martin et al. 1973; Sakurai et al. 1974), also leading to cochlear dysfunction with subsequent hearing loss (Kamphoven et al. 2004). In patients with clinical symptoms suggestive for Pompe disease, diagnosis is based on marked reduction of GAA activity in purified peripheral blood lymphocytes (Winchester et al. 2008). In general, GAA enzyme activity in fibroblasts of <1% of that of normal controls is associated with rapid disease progression, as seen in the infantile form, whereas in the late onset forms, GAA activity ranges from 2% to 40% of normal controls, and disease progression is much slower. Incidence data are limited, with reports ranging from 1:300,000 to 1:14,000 livebirths (Hirschhorn and Reuser 2001). A recent study, however, testing for Pompe disease by newborn screening resulted in a prevalence of 1:33,333 in Taiwan (Chien et al. 2008). In all disease variants, morbidity and mortality is high (Kishnani and Howell 2004), and for decades, treatment was limited to supportive care. It was only in 2006 that enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) was approved for commercial use in North America and Europe

and yielded promising results, particularly in patients with infantile Pompe disease.

Early intervention with ERT is essential to reverse cardiomyopathy and to halt motor disease progression. In addition, it was hypothesized from the first clinical trials that the presence or absence of cross-reactive immunological material (CRIM) may affect prognosis (Amalfitano et al. 2001). CRIM-negative patients are completely unable to form any precursor form of native enzyme, whereas patients who are able to produce some precursor form of abnormal- or normal-size native enzyme are CRIM-positive. Kishnani et al. reported that CRIM-negative status predicted reduced overall survival and invasive ventilator-free survival and poorer motor development in ERT-treated infants with Pompe disease (Kishnani et al. 2010). The effect of CRIM status was hypothesized to be mediated by antibody response to exogenous protein (Kishnani et al. 2007; Kishnani et al. 2010; Kishnani et al. 2006b). Induction of immune modulation to eliminate antibodies in a CRIM-negative patient was first reported through intravenous administration of gamma globulin, anti-CD20 monoclonal antibody (rituximab), and methotrexate (Mendelsohn et al. 2009) and proved to be a promising approach to overcome poor prognosis in CRIM-negative patients (Kishnani et al. 2010).

Here we report on a 44-month follow-up of a CRIM-negative patient with infantile Pompe disease started on ERT early, subsequently including anti-immunoglobulin E (anti-IgE) antibody (omalizumab) treatment from the age of 6 months due to severe IgE-mediated allergic reactions to Myozyme. To the best of our knowledge, this is the first report of a CRIM-negative patient on ERT and monoclonal anti-IgE antibody. In the patient described in this report, application of omalizumab was ensued by immunomodulatory effects, as indicated by sustained low titers of rhGAA-IgG; such unforeseen effects of anti-IgE antibodies beyond neutralization of IgE might deserve further investigation.

### Case report

This now 44-month-old child of consanguineous Turkish parents (first-degree cousins) was born after an uneventful pregnancy. The mother was raised in Switzerland and speaks German fluently; the father immigrated to Switzerland at the age of 6 years and speaks and understands German. At the age of 4 weeks, a heart murmur was noted at a routine checkup and further investigations showed a hypertrophic cardiomyopathy. Neurological examination revealed mild axial, facial, and proximal weakness. Pompe disease was suspected and confirmed by the absence of detectable serum GAA activity in leukocytes and fibroblasts and a homozygous mutation (c.1157insA) in the *GAA* gene; both parents are

carriers for this mutation. Our patient tested CRIM-negative (determined in cultured fibroblasts by a qualitative Western blot assay prior to ERT; Genzyme, Laboratory, Westborough, MA, USA). At the age of 8 weeks, ERT was started with Myozyme® at a recommended dose of 20 mg/kg every 2 weeks for 3 months. Subsequently, the dose and frequency of ERT had to be changed to 10 mg/kg weekly due to type III allergic reactions; in addition, pretreatment with intravenously applied corticosteroid and antihistaminic drugs was begun, combined with a decreased infusion rate. Due to persistent, severe life-threatening allergic reactions that were not controllable with corticosteroids, antihistaminic drugs, or decreased infusion rate, the regime was optimized by adding omalizumab, a recombinant monoclonal antibody against IgE, at the age of 6 months. A

scratch skin test for Myozyme tested positive as well as specific for Myozyme IgE hypersensitivity in a blood sample (Genzyme). One year later, ERT intervals could be extended to 14 mg/kg every 10 days and the antiallergic treatment was successfully weaned with the exception of omalizumab. Recombinant human GAA IgG antibody titers were measured routinely every 4–5 months and were always <1:800 (Table 1).

#### Response to treatment

Auditory function, cognitive and motor milestones, and behavior were evaluated at 12-month intervals. The progress of myelination was investigated by brain magnetic resonance imaging (MRI). Cardiac function was monitored

**Table 1** Response to enzyme replacement therapy (ERT)

	At diagnosis	6 months on ERT	12–18 months on ERT	30 months on ERT	44 months on ERT
Cardiac involvement					
LVM g/m <sup>2</sup> ( <i>n</i> 42–95)	165	87	83	55	50
EF in %	48			52	55
Muscle weakness		Sits	Walks, climbs	Runs, jumps, no Gowers	Runs, jumps, no Gowers
Proximal weakness	M4	Months 4	Months 4–5	Months 4–5	Months 4–5
Facial and axial weakness	Mild	Months 3	Month 3	Months 3+	Months 3+
Cognitive development	Age appropriate	Griffith-Test age at 8 months	Griffith test at 18 m:	Bayley test at age 32 months	SONER test at age 44 months
		Locomotor 7 months	Locomotor 16.5 m	DA 22 months/DQ 70–75	DA 35 months/DQ 70–75
		Eye and hand 8 months	Eye and hand 15.5 m	Nonverbal best item 26 m	Nonverbal best item 39 months
			Hearing/language 14.5 m	Very short attention span	Very short attention span
			Personal-social 16 m	No spoken words	1 spoken word
			Performance 17 m	Behavioural problems	Behavioural problems
Hearing					
Otoacoustic emissions	Failed				
Auditory brainstem response (thresholds dB)		80–90 bB			
Behavioral audiometry high frequencies			40 dB	40 dB	40 dB
Behavioral audiometry low frequencies			60–70 dB	60–70 dB	60–70 dB
Hearing aids				+	+
Myozyme antibody testing					
IgG	Negative	Negative	Positive	Positive	Positive
Titer	N/A	N/A	1:400	1:400	1:400

*LVM* left ventricular mass measured by echocardiography, *EF* ejection fraction calculated by cardiac magnetic resonance imaging (MRI), *DA* developmental age, *DQ* developmental quotient, *N/A* not available

by echocardiography every 4 months and in addition by a cardiac MRI at diagnosis and at the age of 33 and 44 months, respectively (Table 1).

**Cardiac** Initially, there was a severe concentric left ventricular hypertrophy with a septum thickness on echocardiography of 9 mm (norm <6 mm) and a left ventricular mass (LVM) on MRI of 162 g/m<sup>2</sup> (norm 84 g/m<sup>2</sup>). Ventricular size and systolic function were normal. At the age of 2 1/2 years, myocardial hypertrophy was resolved. At the age of 3 1/2 years, left ventricular end-diastolic volume was 68 ml/m<sup>2</sup>, right ventricular end-diastolic volume 59 ml/m<sup>2</sup>, and LVM was 50 g/m<sup>2</sup> on MRI.

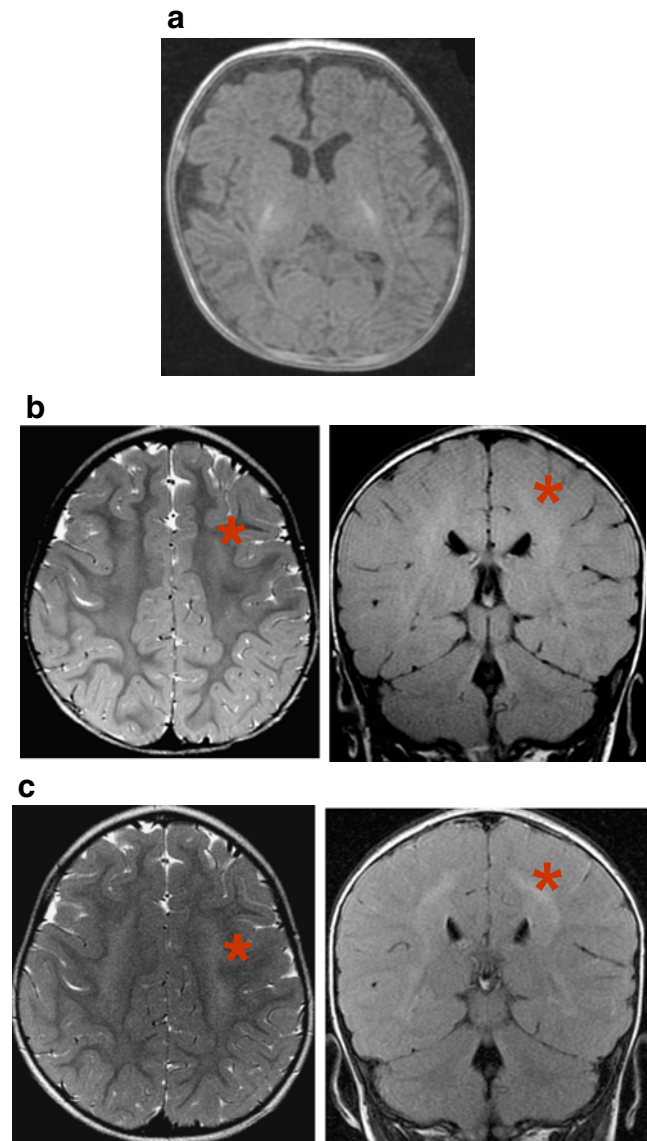
**Respiratory** No respiratory involvement was detectable by yearly polysomnography, and no respiratory insufficiency occurred during two episodes of bacterial pneumonia.

**Muscle weakness** Gross motor development and muscle strength was almost normal, except for facial and neck flexor muscles. At the age of 44 months, she had some fatigability and ataxia.

**Cognitive development** The patient was only 5 weeks old at diagnosis and was age appropriate on the Griffith Scale. After 6 months of ERT, there was no significant delay in the locomotor and eye and hand subtests of the Griffith scale, although the girl was difficult to test at that age because of relevant allergic reactions and side effects of the antihistaminic medication; at age 18 months, there was marked delay in speech and language development but also delay in fine-motor tasks and social behavior in the Griffith test. At the age of 32 months, her overall developmental age was 22 months in the Bayley test. In addition, she had a markedly reduced attention span, behavioral problems such as aggressiveness and repetitive behavior, and delays in expressive language and speech development. Nonverbal development test SON-R revealed a developmental age of 35 months at the chronological age of 44 months; delays in expressive language and speech development had not improved significantly when compared with the age of 32 months.

**Hearing** The patient failed newborn hearing screening with otoacoustic emissions, but clinically, she responded to sounds. At 8 months of age re-evaluation by auditory brainstem response (ABR) showed hearing thresholds on both ears of 80–90 dB, and she responded as type B at the time on tympanometry. After improvement of the middle ear situation by paracentesis on both ears, behavioral audiometry revealed that a hearing loss of 40 dB in the low frequencies and 60–70 dB in the high frequencies remained. In the following months, at the age of 26 months, hearing aids were fitted that were well tolerated, and speech

and language therapy as well as orofacial therapy was initiated. In free-field audiometry, the thresholds with hearing aids were measured at 20–25 dB. During therapy sessions, prompt reactions also to sounds with low intensity were observed. Despite weekly auditory–verbal, speech, and language therapy and regularly checking the fitting of the hearing aids, the expressive language development



**Fig. 1** Brain magnetic resonance imaging (MRI) on enzyme replacement therapy (ERT) on follow-up showing white matter changes appearing at the age of 20 months compared with MRI at diagnosis. At the age of diagnosis (**a**), T-1 axial with normal age-appropriate images showing normal myelination. At the age of 20 months (**b**): on the *left*, axial T-2 image; on the *right*, coronal fast low-angle inversion recovery (FLAIR) image. Changes in white matter, sparing U fibers (\*); MRI at 32 months (**c**): on the *left*, axial T-2 image; on the *right*, coronal FLAIR image. In comparison with **b**, increased white matter signal intensity (\*)



remain delayed, in both Turkish and German, and articulation is still difficult and limited to some vowels.

**Brain imaging** Before initiation of ERT, myelination was age appropriate. Yearly MRI at age 1 1/2, 2 1/2, and 3 1/2 years showed signal alterations in the white matter on T2 and fast low-angle inversion recovery (FLAIR) images with sparing of U fibres. Myelination had progressed appropriately. In the repeat scan at age 2 1/2 and 3 1/2 years, respectively, signal alterations on FLAIR images and T2 markedly progressed (Fig. 1).

## Discussion

We report almost normal motor milestones and normalization of cardiac function in a CRIM-negative infantile Pompe disease patient up to the age of 44 months. Despite an excellent response of skeletal and cardiac muscle, we noted progressive white matter changes on MRI associated with a delay in cognitive, speech and language development, as well as hearing loss and behavior impairment.

Very little is known about the long-term cognitive development of patients with infantile Pompe disease independent of rhGAA CRIM status. Furthermore, there are only a few reports on brain imaging in infants with classic Pompe disease. This may be attributed to the early mortality usually observed in untreated patients, the lack of close monitoring OF CNS parameters due to the historical endpoints chosen to prove the efficacy of ERT (Amalfitano et al. 2001; Kishnani et al. 2006b, 2007; Klinge et al. 2005; Van den Hout et al. 2001, 2004), or to difficulties of cognitive testing and the risk of sedation for MRI in patients on ERT who may still have significant respiratory muscle weakness and/or cardiomyopathy. Furthermore, it also became evident that not all patients responded equally well to ERT regarding motor development, and it has been shown that this is dependent on CRIM status and hypothesized to be directly mediated by antibody response to ERT (Kishnani et al. 2010).

The motor development of our CRIM-negative patient was only slightly late; however, acquisition of motor milestones was within normal limits and gain of motor milestones is continuing. Muscle weakness significantly improved over the course on ERT, predominantly being limited to facial and neck flexor muscles; however, cognitive testing using Griffith and Bayley scales and SON-R indicated a deviation from age-appropriate development; speech and language development were markedly delayed, and behavioral issues were noted. Behavior impairment in Pompe disease was only reported in a mouse model (Sidman et al. 2008).

Only recently has it been reported that overall language delay in infantile Pompe patients on ERT is common, with a high risk of speech disorder caused by velopharyngeal dysfunction and deficits in the orofacial mechanism; however, overall language delays tended to improve or remain stable over time (Muller et al. 2009). In addition, hearing loss in Pompe disease is known; it is thought to be caused by glycogen storage in the organ of Corti (Kamphoven et al. 2004). Despite hearing aids for >12 months in our patient, speech and language therapy, as well as orofacial stimulation therapy, we did not note any improvement over the period of time. At the age of 44 months, our patient did not speak any words and had a nasal voice. Testing showed that nonverbal skills were better compared with verbal. Audiology assessment showed a moderate hearing loss but not severe enough to explain all the language developmental problems. There is no family history of cognitive or speech problems; both parents have high school certificates and speak German and Turkish fluently.

Brain MRI in our patient clearly reflects brain involvement, particularly in the white matter. We speculate that these MRI findings might explain the cognitive and most likely the behavioral impairment; there is no evidence for a disorder other than Pompe disease resulting in white matter changes, although this might be a possibility in the context of consanguinity. Little is known about possible side effects of omalizumab; however, current data do not show evidence for white matter changes in a small group of treated patients.

It has been clearly shown in the literature, however, that untreated Pompe disease may also present with CNS involvement. Several early and also more recent studies (Burrow et al. 2010; Chen et al. 2004; Crome et al. 1963; Engel et al. 1973; Gambetti et al. 1971; Lee et al. 1996; Mancall et al. 1965; Martin et al. 1973) point to abnormalities in the CNS and PNS, leading to a slowly progressive neurodegenerative process. Chien et al. reported myelination delay on MRI in five patients started on ERT later than 5.5 months of age (Chien et al. 2006). However, initial brain MRI was performed late, all but one patient had significant motor developmental delays, and no information regarding CRIM status, speech and language development, or hearing was provided.

Due to severe allergic reaction with positive testing for anti-Myozyme IgE, a recombinant monoclonal antibody against IgE (omalizumab) was added to the regime for our patient. Interestingly, anti-rhGAA IgG antibody titers remained low (1:400) during the entire follow-up period despite the CRIM-negative status. Anti-rhGAA IgG antibody titers are generally reported higher in CRIM-negative patients (median peak titers 1:204,800) compared with CRIM-positive patients (median peak titers 1:1,800) (Kishnani et al. 2010). We hypothesize that the monoclonal anti-IgE antibody used in this patient did not only halt further allergic

reactions but unexpectedly might have also played an important role as an immune modulator and thereby may have contributed to the favorable motor outcome. We consider this to be an interesting and important observation. Although the underlying immunological mechanism is not understood and the observation is based on a single case, we suggest that omalizumab may be of benefit for patients with IgE-mediated allergic reaction. Only long-term studies on a larger patient population will help clarify a possible role and the risk–benefit profile of this biological agent.

To the best of our knowledge our report describes for the first time continuous motor milestones gain in a CRIM-negative infantile Pompe disease patient on ERT over the course of 44 months. However, the progressive white matter changes on MRI associated with a delay in cognitive development highlights the importance of close neurological follow-up in treated patients with Pompe disease.

The significance of nervous system involvement in longer survival in infantile Pompe disease patients is far from clear. Further studies to confirm and extend these findings are necessary, as they might have major implications regarding the management and long-term prognosis, in particular for CRIM-negative infantile Pompe disease patients on ERT. The findings of possible CNS involvement despite ERT, however, opens up the field for ethical discussions concerning the early start of ERT and newborn screening for Pompe disease, as well as on the emerging controversial debate about the cost-effectiveness of ERT in lysosomal storage disorders.

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